SCREENING-LEVEL HAZARD CHARACTERIZATION

Cashew, Nutshell Liquid
(CASRN 8007-24-7)

The High Production Volume (HPV) Challenge Program[1] was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance[2,3] and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT's focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental

[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.

authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and information previously not readily available to the public.

Chemical Abstract Service Registry Number (CASRN)	**8007-24-7**
Chemical Abstract Service Name	**Cashew, nutshell liquid**
Structural Formula	Mixture of anacardic acid, cardanol, and cardol (see Section 1)

Summary

This chemical is a liquid with low water solubility and low vapor pressure. It is expected to have low mobility in soil. Volatilization of cashew nutshell liquid is considered low to moderate. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered rapid. It is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The acute hazard to fish, aquatic invertebrates, and aquatic plants is based on estimated toxicity values for cardanol of 0.001 mg/L, 0.004 mg/L, and 0.010 mg/L, respectively.

Acute oral toxicity of this chemical in rats is low. It is a dermal sensitizer in guinea pigs. An oral combined repeated-dose/reproductive/developmental screening study in rats showed histopathological effects on the lung and lymph nodes, and hematological effects in adult animals at a dose of 1000 mg/kg-day; the NOAEL for systemic toxicity was 150 mg/kg-day. In the same study, there was reproductive toxicity at 1000 mg/kg-day as demonstrated by an increase in dyctocia; the NOAEL for reproductive toxicity was 150 mg/kg-day. There was no evidence of developmental toxicity in this study and the NOAEL was 1000 mg/kg-day. This chemical did not induce gene mutations or chromosomal aberrations when tested *in vitro*.

The acute toxicity for aquatic organisms is considered a data gap under the HPV Challenge Program.

The sponsor, Cardolite Corporation, submitted a Test Plan and Robust Summaries to EPA for Cashew Nutshell Liquid (CAS No. 8007-24-7; 9th CI Name: Cashew Nutshell Liq.) on June 5, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on June 5, 2002 (http://www.epa.gov/chemrtk/pubs/summaries/casntliq/c13793tc.htm). EPA comments on the original submission were posted to the website on November 12, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on December 20, 2002, November 2, 2006 and April 6, 2007, which were posted to the ChemRTK website on January 21, 2003, November 16, 2006 and July 24, 2007, respectively.

1 Chemical Identity

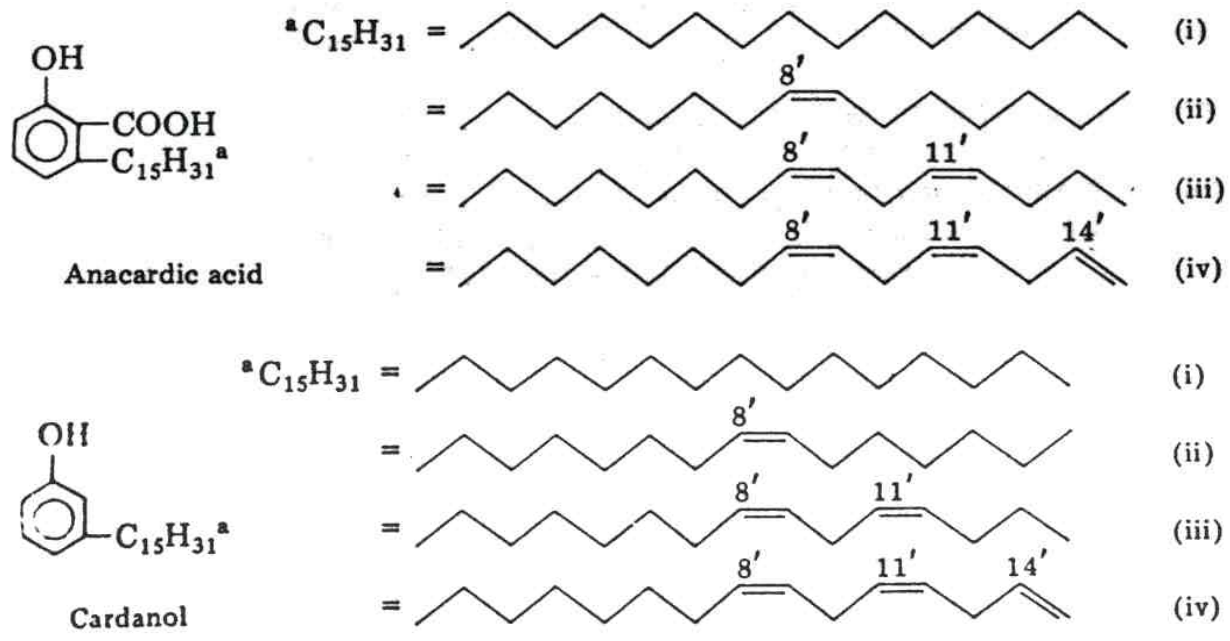
1.1 Identification and Purity

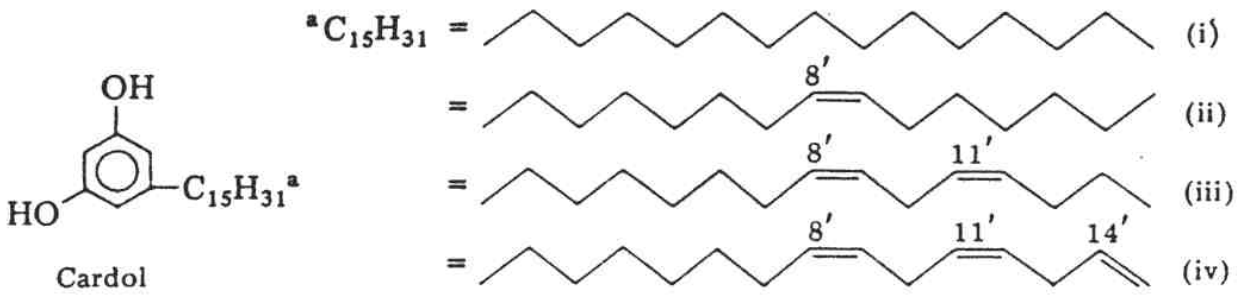
The following description is taken from the final Test Plan (2006):

Cashew nutshell liquid is obtained from the shell of a cashew nut and is a source of naturally occurring phenols. About 30-35% of this chemical is present in the shell, which amounts to approximately 67% of the nut. Cashew nutshell liquid is traditionally obtained as a by-product during the process of removing the cashew kernel from the nut.

Natural (i.e. cold, solvent extracted) cashew nutshell liquid is a liquid that contains approximately 70% anacardic acid, 18% cardol, and 5% cardanol (Fig 1), with the remainder being made up of other phenols and less polar substances. Anacardic acid, cardanol and cardol consist of mixtures of components having various degrees of unsaturation in the alkyl side-chain.

Figure 1: Structures of Anacardic acid, Cardanol and Cardol





In technical (i.e. heat extracted) cashew nutshell liquid, the heating process leads to decarboxylation of the anacardic acid to form cardanol. Typically, the composition of technical cashew nutshell liquid is approximately 52% cardanol, 10% cardol, 30% polymeric material, with the remainder being made up of other substances. The technical cashew nutshell liquid is often further processed by distillation at reduced pressure to remove the polymeric material. The composition of distilled technical cashew nutshell liquid (Cardolite NC 511) is approximately 78% cardanol, 8% cardol, 2% polymeric material, < 1% 2-methyl cardanol, 2.3% heptadecyl homologue triene, 3.8% heptadecyl homologue diene and the remainder other homologous phenols.

1.2 Physical-Chemical Properties

The physical-chemical properties of cashew nutshell liquid are summarized in Table 1. Cashew nutshell liquid is a liquid with low water solubility and low vapor pressure.

Table 1. Physical-Chemical Properties of Cashew Nutshell Liquid[1]

Property	**Value**
CASRN	8007-24-7
Molecular Weight	298-320
Physical State	Liquid
Melting Point	Liquid at room temperature
Boiling Point	Polymerizes and decomposes prior to boiling[3]
Vapor Pressure	3.8×10^{-7} mm Hg at 25°C (measured)
Water Solubility	0.305 mg/L at 20°C (measured)
Dissociation Constant (pK_a)	~10.06 (estimated)[2]
Henry's Law Constant	2.6×10^{-10}–9.7×10^{-5} atm-m^3/mole (estimated)
Log K_{ow}	>6.2 (measured)

[1]Cardolite Corporation, Inc. November 2, 2006. Revised Robust Summary and Test Plan for Cashew Nutshell Liquid. http://www.epa.gov/chemrtk/pubs/summaries/casntliq/c13793tc.htm.
[2]SPARC. 2008. Online pK_a and Property Calculator v. 4.2.1405-s4.2.1408. Accessed September 7, 2008. http://ibmlc2.chem.uga.edu/sparc/index.cfm?CFID=32727&CFTOKEN=65477992.
[3] BP 225 °C @ 10 mm Hg US Patent 2,098,824

2 General Information on Exposure

2.1 Production Volume and Use Pattern

Cashew, nutshell liquid had an aggregated production and/or import volume in the United States of 50 to 100 million pounds during calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include intermediates in the manufacture of other basic organic chemicals. Non-confidential information in the IUR indicated that the commercial and consumer products containing the chemical include automotive care products. The HPV submission states that the chemical is primarily used in antioxidants, plasticizers and processing aids for rubber compounds and modifiers for plastic materials. Cashew nutshell liquid resins have been used extensively in the manufacture of friction-resistant components in applications such as brake and clutch linings.

2.2 Environmental Exposure and Fate

No quantitative information is available on releases of this chemical to the environment.

The environmental fate properties are provided in Table 2. Cashew nutshell liquid is expected to have low mobility in soil. Cashew nutshell liquid was shown to be readily biodegradable using a modified Sturm test (OECD 302D). The rate of volatilization of cashew nutshell liquid from water and moist soil is considered low to moderate. The rate of hydrolysis is considered negligible under environmental conditions. Cashew nutshell liquid is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 2. Environmental Fate Characteristics of Cashew Nutshell Liquid[1]

Property	**Value**
Photodegradation Half-life	0.351–1.254 hours (estimated)
Hydrolysis Half-life	Stable
Biodegradation	96% after 28 days (readily biodegradable)
Bioconcentration	BCF = 4.5 (estimated)
Log K_{oc}	7.5–8.6 (estimated)
Fugacity (Level III Model; simultaneous 1,000 kg/hour emission to air, water, and soil compartments)	Air = 0% Water = 1.86% Soil = 30.9 % Sediment = 67.2%
Persistence[2]	P1 (low)
Bioaccumulation[2]	B1 (low)

[1]Cardolite Corporation, Inc. November 2, 2006. Revised Robust Summary and Test Plan for Cashew Nutshell Liquid. http://www.epa.gov/chemrtk/pubs/summaries/casntliq/c13793tc.htm.
[2]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

3 Human Health Hazard

Acute Oral Toxicity

Acute toxicity data conducted according to established guidelines were not submitted. However, during a range-finding study for the combined toxicity study (see below), Sprague-Dawley rats (3/sex/dose) were orally dosed with 0 or 1,000 mg/kg-bw/day for 14 days. No mortality occurred during the 14 day observation period. No clinically observable signs of toxicity were observed. No macroscopic abnormalities were observed at necropsy.
LD_{50} > 1000 mg/kg-bw (14 daily exposures-only one dose tested)
Repeated-Dose Toxicity

In a combined repeated-dose/reproductive/developmental toxicity screening test, groups of Sprague-Dawley rats (10 sex/dose) were dosed via gavage daily at 0, 15, 150, or 1000 mg/kg-bw/day for up to 49 days. Increased salivation was noted in animals of both sexes at the high-dose level after day 9. Two high-dose females had deaths attributed to dystocia, slow or difficult labor; one was euthanized on day 21 and another found dead on day 22. High-dose females had statistically significant increased relative liver weights. High-dose males had statistically significant decrease in absolute brain weights. Hematological changes (elevated platelet, hemoglobin, erythrocyte, and hematocrit counts, elevated mean cell volume, and decreased mean cell hemoglobin concentration) were noted in high-dose males. An increase in mean cell volume was also noted in high-dose females. Clinical biochemistry changes (elevated aspartate and alanine aminotransferases, alkaline phosphatase, and inorganic phosphorus, reduction in cholesterol and elevated bilirubin) were noted in males and females at the high dose. High-dose males also had increased plasma urea, reduced glucose levels, and elevated albumin/globulin ratios. The significance and magnitude of changes are not noted. Histopathological changes at the high dose included higher incidence of alveolar macrophages in the lungs in females, abnormal multiplication of macrophages and/or foamy macrophages in the lymph nodes and overgrowth of the lining of the forestomach in both sexes, and thickening of the lining of the small intestine in males.
LOAEL = 1000 mg/kg-bw/day (based on effects to the lungs, lymph nodes, and hematology)
NOAEL = 150 mg/kg-bw/day

Reproductive/Developmental Toxicity

In the combined repeated-dose/reproductive/developmental toxicity screening test described previously, no adverse effects were reported on mating performance, fertility, precoital interval, duration of gestation, gestation index, number of implantations, or number of corpora lutea. In the high-dose dams, 2/10 had deaths attributed to dystocia, slow or difficult labor, on day 21 and 22. An additional dam in this group died for unexplained reasons (assume gavage error) at a time not specified. No treatment related changes were noted in litter size, weight, sex ratio, viability index, post-natal growth rate or toxicologically significant effects on offspring.
LOAEL (reproductive toxicity) = 1000 mg/kg-bw/day (based on deaths due to slow/difficult labor)
NOAEL (reproductive toxicity) = 150 mg/kg-bw/day

NOAEL (developmental toxicity) = 1000 mg/kg-bw/day (based on no effects at the highest dose tested)

Genetic Toxicity – Gene Mutation

In vitro
(1) In bacterial reversion assays, *Salmonella typhimurium* strains (TA98, TA100, TA1535, TA1537 and TA1538) were exposed to cashew nutshell liquid at concentrations of 50, 150, 500, 1500 or 5000 µg/plate in the presence and absence of metabolic activation. Three replicates were conducted per experiment. No cytotoxicity was noted at the maximum concentration of 5000 µg/plate. A precipitate was observed at 1500 and 5000 µg/plate but it did not impact the scoring of colonies. No significant increase in the frequency of revertant colonies was recorded for any of the bacterial strains at any concentration, either with or without metabolic activation. Positive and solvent controls were tested and responded appropriately.
Cashew nutshell liquid was not mutagenic in this assay.

(2) In forward mutation assays, Chinese hamster ovary (CHO-KI BH4) cells were exposed to cashew nutshell liquid, in two experiments, in the presence and absence of metabolic activation. In experiment 1 the concentrations ranged from 0.75 – 18 µg/mL and in the second experiment, the concentration range was and 0.75 – 24 µg/mL. Two replicates were conducted per experiment. Positive and solvent controls were tested and responded appropriately. The cytotoxic concentration with and without metabolic activation was 47.19 µg/mL (in the text, though the tables stated 24 µg/mL was toxic with activation). The test substance did not induce significant or dose-related mutant frequency in the presence or absence of metabolic activation in either of the two experiments.
Cashew nutshell liquid was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro
In a chromosomal aberration test, human lymphocytes were exposed to cashew nutshell liquid in the presence and absence of metabolic activation in three experiments. The concentration ranges were 3 – 25 µg/mL, 0.78 – 37.5 µg/mL and 3.125 or 25 µg/mL in the first, second and third experiments, respectively. Harvest time for the cells was 20 hours for experiments 1 and 2, and 44 hours for experiment 3. Two replicates were conducted for each experiment. Positive and solvent controls were tested which responded appropriately. The cytotoxic concentrations were 12.5 µg/mL with metabolic activation and > 25 µg/mL without metabolic activation. The test substance did not induce a significant increase in the frequency of cells with chromosome aberrations or polyploid cells in either the presence or absence of metabolic activation.
Cashew nutshell liquid did not induce chromosomal aberrations in this assay.

Additional Information

Skin Sensitization

In an assay using albino Dunkin Hartley guinea pigs (20 females/dose), intra-dermal induction was conducted using 1% (w/v) in liquid paraffin and 1% (w/v) in a mixture of Freund's complete adjuvant plus distilled water. Topical induction was conducted using 25% (v/v) in liquid paraffin. Topical challenge was conducted with 5% or 2% (v/v) in liquid paraffin. Following intra-dermal induction, well defined, moderate to severe erythema was seen at 24- and 48-hour observations periods. Skin reactions observed at 24 and 48 hours after 5% topical challenge dose included very slight to well-defined erythema and very slight edema and desquamation. Very slight erythema in one animal and desquamation in three animals was present at 72 hours at the 2% challenge dose. All animals showed an expected gain in body weight over the study period. The test substance produced a 70% (14/20) sensitization rate in the study and was classified as a "strong" sensitizer.
Cashew nutshell liquid was sensitizing in this assay

Conclusion: Acute oral toxicity of this chemical in rats is low. It is a dermal sensitizer in guinea pigs. An oral combined repeated-dose/reproductive/developmental screening study in rats showed histopathological effects on the lung and lymph nodes, and hematological effects in adult animals at a dose of 1000 mg/kg-day; the NOAEL for systemic toxicity was 150 mg/kg-day. In the same study, there was reproductive toxicity at 1000 mg/kg-day as demonstrated by an increase in dyctocia; the NOAEL for reproductive toxicity was 150 mg/kg-day. There was no evidence of developmental toxicity in this study and the NOAEL was 1000 mg/kg-day. This chemical did not induce gene mutations or chromosomal aberrations when tested *in vitro*.

4 Hazards to the Environment

The sponsor did not submit measured aquatic toxicity data for cashew nutshell liquid, but provided data for log K_{ow} and water solubility. ECOSAR (v. 1.00a) was used to assess acute aquatic toxicity of cardanol (CASRN 37330-39-5), the primary component of the sponsored distilled technical grade cashew nutshell liquid, which is a mixture of primarily cardanol (78%) and cardol (8%; CASRN 57486-25-6).

Acute Toxicity to Fish

A 96-hour LC_{50} value for fish exposed to cashew nutshell liquid was estimated by ECOSAR v. 1.00a.
96-h LC_{50} = 0.001 mg/L (estimated)

Acute Toxicity to Aquatic Invertebrates

A 48-hour EC_{50} value for *Daphnia* exposed to cashew nutshell liquid was estimated by ECOSAR v. 1.00a.
48-h EC_{50} = 0.004 mg/L (estimated)

Toxicity to Aquatic Plants

A 96-hour LC_{50} value for algae exposed to cashew nutshell liquid was estimated by ECOSAR v. 1.00a.

96-h LC_{50} = 0.010 mg/L (estimated)

Conclusion: The acute hazard to fish, aquatic invertebrates, and aquatic plants is based on estimated toxicity values for cardanol of 0.001 mg/L, 0.004 mg/L, and 0.010 mg/L, respectively..

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL Cashew Nutshell Liquid (CASRN 8007-24-7)**
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC_{50} (mg/L)	0.001 (estimated)
Aquatic Invertebrates 48-h EC_{50} (mg/L)	0.004 (estimated)
Aquatic Plants 72-h EC_{50} (mg/L)	0.010 (estimated)
Summary of Human Health Data	
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**>1000**
Repeated-Dose Toxicity NOAEL/LOAEL (mg/kg-bw/day)	**NOAEL = 150 LOAEL = 1000**
Reproductive/Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day) Reproductive Toxicity	**NOAEL = 150 LOAEL = 1000**
Developmental Toxicity	**NOAEL = 1000**
Genetic Toxicity – Gene Mutation *In vitro*	**Negative**
Genetic Toxicity – Chromosomal Aberrations *In vitro*	**Negative**
Additional Information – Skin Sensitization	**Positive**